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PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 56613-PCT/JP	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. PCT/US99/23245	International filing d: *(day/month/year)* 05 OCTOBER 1999	(Earliest) Priority Date *(day/month/year)* 05 OCTOBER 1998

Applicant
THE TRUSTEES OF COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 7 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. [ ] **Certain claims were found unsearchable** (See Box I).

2. [X] **Unity of invention is lacking** (See Box II).

3. [ ] The international application contains disclosure of a nucleotide and/or amino acid sequence listing and the international search was carried out on the basis of the sequence listing
   - [ ] filed with the international application.
   - [ ] furnished by the applicant separately from the international application,
     - [ ] but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
   - [ ] transcribed by this Authority.

4. With regard to the title,
   - [X] the text is approved as submitted by the applicant.
   - [ ] the text has been established by this Authority to read as follows:

5. With regard to the abstract,
   - [ ] the text is approved as submitted by the applicant.
   - [X] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is:
   Figure No. _____
   - [ ] as suggested by the applicant.
   - [ ] because the applicant failed to suggest a figure.
   - [ ] because this figure better characterizes the invention.
   - [X] None of the figures.

Applicant: Ann Marie Schmidt and David Stern
Serial No.: 09/166,649
Filed: October 5, 1998
Exhibit D

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/23245

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-13 and 15-29

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Box III TEXT OF THE ABSTRACT (Continuation of item 5 of the first sheet)

The abstract is too long (PCT Rule 8.1(b)). The abstract must be less than 150 words, or 200 words when no Figure is to be published.

NEW ABSTRACT

The present invention provides a method for determining whether a compound is capable of inhibiting the interaction of a peptide with receptor for advanced glycation end product (RAGE), which comprises: (a) admixing: (i) the peptide, wherein amino groups of the peptide are inactivated by derivitization, (ii) RAGE or a fragment thereof, and (iii) the compound; (b) determining the amount of the peptide bound to RAGE or the fragment thereof, and (c) comparing the amount of bound peptide determined in step (b) with the amount determined when the peptide is admixed with RAGE or a fragment thereof in the absence of the compound, thereby determining whether the compound is capable of inhibiting the interaction of the peptide with RAGE or a fragment thereof, wherein a reduction in the amount of binding in tyhe presence of the compound indicates that the compound is capable of inhibiting the interaction.

INTERI 'IONAL SEARCH REPORT

International application No.
PCT/US99/23245

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : C07K 14/705, 17/00; G01N 33/50

US CL : 530/350, 402; 436/7.1; 435/7.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 530/350, 402; 436/7.1; 435/7.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

West 1.2, STN/CAS ONLINE, Medline, Biosis, Embase, Caplus

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X - Y	WO 97/26913 A1 (THE TRUSTEES OF COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK) 31 July 1997 (31/7/97), see entire document, especially abstract, page 13 lines 11-33, and claims 49-68.	1,2, 15-21, 29 ----- 3-13, 22-28
A	MACKIC et al. Human Blood-Brain Barrier Receptors for Alzheimer's Amyloid-B 1-40. Journal of Clinical Investigation. August 1998, Vol. 102, No.4, pages 734-743.	1-13, 15-29
A	BUCALA et al. Modification of Low Density Lipoprotein by Advanced Glycation End Products Contributes to the Dyslipidemia of Diabetes and Renal insufficiency. Proceedings of the National Academy of Sciences. September 1994, Vol. 91, pages 9441-9445.	1-13, 15-29

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 03 JANUARY 2000	Date of mailing of the international search report 10 FEB 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer EILEEN B. O'HARA Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERN IONAL SEARCH REPORT

International application No.
PCT/US99/23245

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P ----- Y,P	US 5,864,018 A (MORSER et al) 26 January 1999 (26/1/99), see column 16, line 30 to column 17, line 54, and claims 1-8.	1, 20,21, 22, 24-28 ------ 2-13, 15-19, 23, 29

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claims 1-13 and 15-29, drawn to a method for determining whether a compound is capable of inhibiting the interaction of a peptide with a receptor for advanced glycation end product.
Group II, claims 14 and 53-57, drawn to a compound of unspecified constitution that is capable of inhibiting the interaction of a peptide with a receptor for advanced glycation end product.
Group III, claims 30 and 31, drawn to a method of assaying whether a compound of unspecified constitution can inhibit a peptide-receptor interaction in a transgenic animal.
Group IV, claims 32-52, drawn to administering to a subject a compound of unspecified constitution in order to inhibit the interaction of an advanced glycation end product with a receptor.

This application contains claims directed to more th... one species of the generic invention. These species are deemed to lack Unity of Invention because they are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for more than one species to be searched, the appropriate additional search fees must be paid. The species are as follows, and
the claims are deemed to correspond to the species listed above in the following manner:
There are seven different groups from which species have to be elected, depending upon which inventions, and the claims encompassing them above, are searched.

If the invention of Group I is selected, one species from each of the following groups must be elected:
1) Type of Peptide: carboxymethyl-modified, carboxymethyl-lysine-modified, or synthetic, as in claims 3, 4 and 5.
2) Derivitization of the peptide: aryl, alkyl, acetyl, propyl, isopropyl, butyl, isobutyl or carboxymethyl, as in claims 9-12.
3) Inhibitory Compound: net negative charge, net positive charge, SRAGE, peptidomimetic, organic molecule, polypeptide, nucleic acid, inorganic molecule, less than 10,000 daltons, antibody, humanized antibody, chimeric antibody, primatized antibody, mutated AGE and mutated RAGE, quinine, derivative of quinine, quinidine or derivative of quinidine, as in claims 14-23 and 49-52.

I the invention of Group II is selected, one species must be chosen for Inhibitory Compound:
3) Inhibitory Compound: net negative charge, net positive charge, SRAGE, peptidomimetic, organic molecule, polypeptide, nucleic acid, inorganic molecule, less than 10,000 daltons, antibody, humanized antibody, chimeric antibody, primatized antibody, mutated AGE and mutated RAGE, quinine, derivative of quinine, quinidine or derivative of quinidine, as in claims 14-23 and 49-52.

If the invention of Group III is selected, one species must be chosen from each of the following:
1) Type of Peptide: carboxymethyl-modified, carboxymethyl-lysine-modified, or synthetic, as in claims 3, 4 and 5.
2) Derivitization of the peptide: aryl, alkyl, acetyl, propyl, isopropyl, butyl, isobutyl or carboxymethyl, as in claims 9-12.
3) Inhibitory Compound: net negative charge, net positive ch...e, SRAGE, peptidomimetic, organic molecule, polypeptide, nucleic acid, inorganic molecule, less than 10,000 daltons, antibody, humanized antibody, chimeric antibody, primatized antibody, mutated AGE and mutated RAGE, quinine, derivative of quinine, quinidine or derivative of quinidine, as in claims 14-23 and 49-52.

If the invention of Group IV is selected, one species must be chosen from each of the following:
3) Inhibitory Compound: net negative charge, net positive charge, SRAGE, peptidomimetic, organic molecule, polypeptide, nucleic acid, inorganic molecule, less than 10,000 daltons, antibody, humanized antibody, chimeric antibody, primatized antibody, mutated AGE and mutated RAGE, quinine, derivative of quinine, quinidine or derivative of quinidine, as in claims 14-23 and 49-52.
4) Disease State: diabetes, systemic lupus erythematosus, inflammatory lupus nephritis, amyloidoses, inflammation, obesity, advanced age or kidney failure, as in claims 37-43 and 53-56.
5) Subjects: human, primate, mouse, rat or dog, as in claim 33.
6) Modes of Administration: intralesional, intraperitoneal, intramuscular injection, intravenous injection, infusion, liposome-mediated delivery, topical, nasal, oral, ocular or otic delivery, as in claim 32.
7) Carriers: diluent, virus, liposome, microencaosule, polymer encapsulated cell, retroviral vector, time release implant, aerosol, intravenous, oral or topical carrier, as in claims 45-48.
The following claims are generic: 1 and 32.

The inventions listed as Groups I-IV do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: Pursuant to 37 C.F.R.§ 1.475(B-D), the ISA/US considers that where multiple products and processes are claimed, the main invention shall consist of the first invention of the category first mentioned in the claims and the first recited invention of each of the other categories related thereto.
Accordingly, the main invention (Group I) comprises the first recited method, a method for determining whether a compound is capable of inhibiting the interaction of a peptide with a receptor. Further pursuant to 37 C.F.R.§ 1.475(B-D), the ISA/US considers that any feature which the subsequently recited products and methods share with the main invention does not constitute a special technical feature within the meaning of PCT Rule 13.2 and that each of such products and methods accordingly defines a separate invention.

The species listed above do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: The molecules of the types of peptides of species group 1, the derivatization of the peptide of species group 2 and the compounds of species group 3 are all distinct molecules with different structures and features. The types of disease states of species group 4, subjects of species group 5, modes of administration of species group 6 and carriers of species group 7 are all different and distinct from each other.

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under Article 19. The Notes are based on the requirements of the Patent Cooperation Treaty and of the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule" and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended ?

The claims only.

The description and the drawings may only be amended during international preliminary examination under Chapter II.

When ? **Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).**

Where not to file the amendments ?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How ? **Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text f one or more of the claims as filed.**

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

What documents must/may accompany the amendments ?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confounded with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

(i) the claim is unchanged;
(ii) the claim is cancelled;
(iii) the claim is new;
(iv) the claim replaces one or more claims as filed;
(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in addi new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amend claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under Article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impa that such amendments might have on the description and the drawings (which cannot be amended unde Article 19(1)).

The statement will be published with the international application and the amended claims.

The statement should be brief, it should not exceed 500 words if in English or if translated into English.

It should not be confounded with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading preferably by using the words "Statement under Article 19(1)."

It should not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

In what language ?

The amendments must be made in the language in which the international application is published. The letter and any statement accompanying the amendments must be in the same language as the international application if that language is English or French; otherwise, it must be in English or French, at the choice of the applicant.

Consequence if a demand for international preliminary examination has already been filed ?

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase ?

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.